Immunisation Subcommittee of the Pharmacology and Therapeutics Advisory Committee (PTAC)

Meeting held on 16 May 2018

(minutes for web publishing)

Immunisation Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.*

Note that this document is not necessarily a complete record of the Immunisation Subcommittee meeting; the relevant portions of the minutes relating to Immunisation Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Immunisation Subcommittee may:

(a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed by PTAC at its meeting on 1 & 2 November 2018, the record of which will be available in due course.

Record of the Immunisation Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 16 May 2018

1 Record of previous subcommittee meeting

1.1 The Subcommittee noted the minutes from the previous meeting held on 26 July 2017. The Subcommittee noted that there were two errors that required amending. These are noted below.

> *9.3 The Subcommittee considered that a 2 + 1 schedule for PCV13 might be an option to consider in the future and noted that there was emerging good quality data regarding this dose schedule.*

1.2 The Subcommittee noted that the above paragraph referred to the incorrect pneumococcal conjugate vaccine. It was agreed the paragraph be amended to replace PCV13 with PCV10. The paragraph would be amended to read:

> *9.3 The Subcommittee considered that a 2 + 1 schedule for PCV10 might be an option to consider in the future and noted that there was emerging good quality data regarding this dose schedule.*

1.3 The Subcommittee noted that there was a typographic error in paragraph 9.26. The Subcommittee considered that the paragraph be amended with the correct spelling of 'herd' immunity, and agreed that the minute be amended to read:

> *9.26 The Subcommittee considered that a universal vaccination campaign to establish herd immunity followed by an infant programme may be a potential strategy to consider for the meningococcal C vaccine.*

1.4 The Subcommittee considered that the remaining minutes were an accurate reflection of the meeting that took place on 26 July 2017.

2 Therapeutic Group Review

Human papillomavirus vaccines (Gardasil and Gardasil 9)

2.1 The Subcommittee noted that supply issues during 2017 and 2018 have had an impact on the distribution patterns of the HPV vaccine. It was noted that supply to school based programmes had been prioritised.

2.2 The Subcommittee noted that it had provided email clinical advice to PHARMAC about the effects of a possible to delay to the administration of the Gardasil 9 final dose for individuals not covered by school based programmes. The Subcommittee considered that a delay of three to four months in delivering the final dose of HPV would not adversely affect the effectiveness of the vaccination. The Subcommittee were supportive of the proposed approach to delay the second and third doses for non-high risk patients by three to four months until new stocks of the vaccine would be available. The Subcommittee considered that high risk immunocompromised individuals should also be prioritised to receive vaccination during the shortage.

Hepatitis B recombinant vaccine

2.3 The Subcommittee noted that there has been an ongoing supply issue for HBvaxPRO adult hepatitis B vaccine 10 mcg per 1 mL. The Subcommittee noted there had been a significant increase in demand in November and December 2017 which was likely to reflect pre-ordering as news of the supply shortage reached vaccinators. The Subcommittee noted that sole supply for HBvaxPRO has been suspended to allow for use of the alternative vaccine Engerix-B 20 mcg.

2.4 The Subcommittee noted that resupply of HBvaxPRO 40 mcg had also been delayed and considered that if a shortage of the 40 mcg strength developed, Engerix-B 20 mcg would be a suitable alternative for dialysis patients and also for liver of kidney transplant patients. The Subcommittee considered that appropriate dose for these patients would be two doses given in one visit.

2.5 The Subcommittee noted that the paediatric 5 mcg strength of HBvaxPRO went out of stock in February 2018, and members had provided email clinical advice to PHARMAC about a suitable replacement. The Subcommittee considered that Engerix-B 20 mcg could be used in place of HBvaxPRO, but noted that it had a larger volume which may cause some additional discomfort to infants.

Bacillus Calmette-Guerin vaccine

2.6 The Subcommittee noted that there has been a long-standing shortage of this vaccine since June 2015. The Subcommittee considered that the BCG vaccine is still relevant in New Zealand and noted that the World Health Organisation (WHO) has recently issued new guidance with better evidence that BCG vaccination is effective. However, the forced cessation of vaccine use in New Zealand has not yet led to observable increases. The Subcommittee noted that recommended usage in New Zealand was based on local knowledge of the baseline risk in New Zealand, rather than WHO guidance. The Subcommittee noted that the last Tuberculosis (TB) surveillance in New Zealand was in 2014. The Subcommittee considered that the current recommendations for BCG vaccination remain appropriate.

2.7 The Subcommittee noted that stock of the BCG vaccine is expected to be available later in 2018 and considered that the initial focus should be on vaccinating those under 6 months of age who meet the funding criteria, are at greatest risk and no testing is required. Members noted no formal catch up programme was planned to recall patients.

Influenza vaccine

2.8 The Subcommittee noted that a quadrivalent vaccine, Influvac Tetra, was funded for the 2018 influenza season. The Subcommittee noted that Influvac Tetra was only indicated for use in people aged three years and over. PHARMAC also funded another quadrivalent vaccine, Fluarix Tetra, for children aged six months to three years of age. The Subcommittee noted that in addition to the Fluarix Tetra stock for young paediatric patients, there was the same quantity again of Influvac (trivalent) vaccine also held in stock as a contingency in case uptake of Fluarix Tetra was higher than expected. The Subcommittee noted that Influvac (trivalent) vaccine is indicated for people aged 6 months and over and use of this vaccine would be appropriate if Fluarix Tetra was not available.

2.9 The Subcommittee noted that influenza vaccine distribution commenced in early April 2018 and that initial quantities of vaccine distribution had been similar to the early stages of previous influenza seasons.

3 Ministry of Health Update

3.1 The Subcommittee noted an update provided by the Ministry of Health Immunisation team regarding completed work and upcoming projects related to the immunisation programme.

4 Influenza vaccines

Application

4.1 The Subcommittee reviewed an influenza vaccine overview paper prepared by PHARMAC staff, a clinician funding application to consider widening access of influenza vaccines and different vaccination strategies, a Ministry of Health strategic direction paper regarding influenza vaccination and correspondence from District Health Boards regarding childhood influenza vaccination. The purpose of the overview paper was to seek the Subcommittee's advice about possible future strategic options for seasonal influenza vaccination. Any funding applications for types of influenza vaccine that are not currently funded would need to be considered at future Subcommittee and PTAC meetings.

Recommendation

4.2 The Subcommittee **recommended** that high dose inactivated influenza vaccine for people aged 65 years and over be included in the next commercial process for influenza vaccine and **recommended** that PHARMAC seek applications from suppliers.

4.3 The Subcommittee **recommended** that adjuvanted inactivated influenza vaccine for people aged 65 years and over be included in the next commercial process for influenza vaccine and **recommended** that PHARMAC seek applications from suppliers.

4.4 The Subcommittee **recommended** that live attenuated influenza vaccine be included in the next commercial process for influenza vaccine and **recommended** that PHARMAC seek applications from suppliers. The Subcommittee **recommended** that access criteria should include children aged 5-12 years.

4.5 The Subcommittee **recommended** that the application for ring protection of high risk groups be declined.

4.6 The Subcommittee **recommended** that widened access to Māori people from an earlier age than 65 years be declined.

4.7 The Subcommittee **recommended** that widened access to Pacific people from an earlier age than 65 years be declined.

Discussion

4.8 The Subcommittee noted that all age groups are affected by influenza, but mortality is higher in those under one year of age and starts to increase for those over 50 years of age. The Subcommittee noted that 2017 hospital discharge rates show that hospitalisation rates are highest for Pacific people, then Māori, European and Asian groups. The rate for Pacific people is approximately three times that for Māori or European.

4.9 The Subcommittee noted that in recent years, approximately 1.2 million doses of influenza vaccine have been distributed each year, which equates to approximately 28% of the population covered. The Subcommittee noted that estimated coverage for high risk groups receiving funded vaccine is approximately 3% for children aged 0-4, 30% for pregnant women and 65% for people aged 65 years or over. Subsets of the 65 year and over group include Māori with 46% coverage and Pacific people with 51% coverage.

4.10 The Subcommittee noted that vaccine effectiveness of inactivated vaccines declines at 8% per month. This suggests that the elderly may have very little protection by 3-4 months after vaccination. The Subcommittee considered that it would be necessary to increase coverage with inactivated influenza vaccines above the current 28% coverage to generate herd immunity. The Subcommittee considered that improving vaccine effectiveness in the elderly would have a greater impact on the elderly.

4.11 The Subcommittee considered a retrospective cohort study by Izurieta et al. Lancet Infect Dis. 2015;15: 293–300 which demonstrated a stronger immune response to a high dose trivalent influenza vaccine (hdTIV) in the elderly compared to a trivalent influenza vaccine (TIV). This study showed hdTIV was 22% more effective in reducing hospitalisations in the elderly, compared to TIV. The Subcommittee considered that hdTIV would provide an additional health benefit to those aged over 65 years and over, with minimal additional risks compared to TIV or quadrivalent influenza vaccine (QIV). Members noted that hdTIV is not currently available in New Zealand. The Subcommittee considered that hdTIV would be likely to work in people 50 years of age and older from an immunological point of view, although data is lacking to support this view and it is not approved for use in people under 65 years of age.

4.12 The Subcommittee considered an observational study of adjuvanted influenza vaccination in an elderly population in Northern Italy by Mannino et al. Am J Epidemiol. 2012;176: 527–533 which showed adjuvanted trivalent influenza vaccine (aTIV) gave a 25% reduction in the risk of hospitalisation. The Subcommittee considered that aTIV would provide an additional health benefit to those aged over 65 years and over, with minimal additional risks compared to a TIV or QIV.

4.13 The Subcommittee noted that live attenuated influenza vaccine (LAIV) is administered intranasally and is indicated for those aged 2-49 years. The Subcommittee considered that LAIV generates a broader immune response than inactivated influenza vaccines. The Subcommittee noted that LAIV has been used in both the US and UK, but there were issues with the H1N1 response in the US and LAIV has not been recommended in the US for the 2017/2018 season. The

Subcommittee noted that more response data is expected be become available over coming influenza seasons, particularly from England.

4.14 The Subcommittee considered that vaccination of primary school age children contributes to herd immunity, protecting high risk individuals who may respond less well to vaccines. The Subcommittee considered that a universal childhood influenza vaccination programme would only be achievable using LAIV, with optimal delivery through a school based programme. The Subcommittee noted that there is currently no registered LAIV product in New Zealand.

4.15 The Subcommittee considered that universal childhood influenza vaccination would provide additional health benefits with minimal additional risks. The Subcommittee considered that additional benefits would include the ability to generate herd immunity, protection of the wider community and reduced hospitalisation of children. The Subcommittee considered that the groups who would benefit most from universal childhood vaccination are the elderly and those with comorbidities. The Subcommittee considered that there is not a particularly high disease burden in school based children. The Subcommittee considered that while vaccinating children may protect other groups, it is an ethical consideration that the children themselves should also derive benefit from the vaccination.

4.16 The Subcommittee considered that there are some groups disproportionately affected by influenza, including Māori, Pacific people, NZ Dep 9-10 deprivation, refugees and asylum seekers. The Subcommittee considered the concept of "risk stacking" for influenza, but noted that data is lacking to support this approach to targeting.

4.17 The Subcommittee considered the concept of "ring protection" ie. the protection of high risk groups by vaccinating close contacts. The Subcommittee considered that ring protection theoretically would provide a health benefit to high risk groups. The Subcommittee noted that only 65% of DHB healthcare workers are vaccinated, but approximately 80% coverage would be required to protect high risk groups. The Subcommittee noted that there is limited evidence supporting the ring fence approach.

4.18 The Subcommittee considered that the introduction of any of hdTIV, aTIV, LAIV or universal childhood vaccination could result in reduced healthcare costs in some years. The Subcommittee considered that if herd immunity was generated, then there would be healthcare savings. The Subcommittee **recommended** that PHARMAC conduct cost effectiveness analysis on universal vaccination compared to childhood school vaccination to achieve herd immunity and bring the results back to a future Subcommittee meeting.

Clinical advice questions from the Ministry of Health

4.19 The Subcommittee considered that the definition of coverage level required to achieve community immunity depends on vaccine effectiveness; and can only ever be partial for influenza. UK data suggests that for school children, 30% coverage achieves indirect protection.

4.20 The Subcommittee considered that it would be more effective to use LAIV in a school based delivery programme, as this would have better user acceptibility. The Subcommittee considered that it would be expensive to implement a school based programme.

4.21 The Subcommittee considered a study by Mannino et al. J Amer Epidemiol 2012 which showed adjuvanted trivalent influenza vaccine (aTIV) gave a 25% reduction in the risk of hospitalisation. The Subcommittee considered that aTIV would provide an additional health benefit to those aged 65 years and over, with minimal additional risks compared to a TIV or QIV.

4.22 The Subcommittee considered a study by Izurieta et al. NEJM 2000 which demonstrated a stronger immune response to a high dose trivalent influenza vaccine (hdTIV) in the elderly compared to a trivalent influenza vaccine (TIV). This study showed hdTIV was 22% more effective in reducing hospitalisations in the elderly, compared to TIV. The Subcommittee considered that hdTIV would provide an additional health benefit to those aged over 65 years and over, with minimal additional risks compared to TIV or quadrivalent influenza vaccine (QIV).

4.23 The Subcommittee considered that there was limited evidence supporting the use of multiple vaccine doses to protect those aged 65 years and over.

4.24 The Subcommittee considered that the observed higher mortality from influenza in Māori and Pacific populations is related to lower coverage in these groups.

4.25 The Subcommittee considered that current coverage of targeted groups is not high, so expanding eligibility to Māori and Pacific from a younger age does not address the low coverage. The Subcommittee considered that increasing coverage was likely to be the best way to protect more Māori and Pacific people.

4.26 The Subcommittee considered that target strategies for particular groups often lead to other inequities. The Subcommittee considered that working towards universal vaccination could be considered, eg. starting with the access for the most deprived groups and then expanding access from there.

5 Meningococcal C Vaccine

Application

5.1 The Subcommittee reviewed analysis conducted by PHARMAC staff that modelled the costs of vaccination against meningococcal C (MenC) for two possible funding scenarios: people living in close living situations and universal childhood vaccination of infants, toddlers, and teenagers.

Recommendation

5.2 The Subcommittee **deferred** making a recommendation regarding the funding of MenC vaccination for people living in close living situations and universal childhood vaccination of infants, toddlers, and teenagers, until more recent epidemiological data can be made available.

Discussion

5.3 The Subcommittee noted that MenC vaccine eligibility was considered by the Immunisation Subcommittee in February 2014 (Immunisation Subcommittee Minutes, February 2014). At that time, a decision regarding widening access to MenC vaccines was deferred, and it was requested that PHARMAC staff assess the effect of funding MenC vaccines for people in close living situations as well as universal vaccination of infants and adolescents.

5.4 The Subcommittee noted that in New Zealand in 2016 there were 75 notified cases of meningococcal disease. Of the 67 strain-typed cases, 70% were serogroup B, 12% were serogroup C, 7% were serogroup W, and 10% were serogroup Y.

5.5 The Subcommittee noted that there was a recent outbreak of MenC in Fiji, with a mass vaccination program planned for Fijians aged 1-19 years. The Subcommittee also noted that the MenC rate has decreased in Australia and the UK following the introduction of vaccination programs, but the incidence of meningococcal W (MenW) disease is increasing.

5.6 The Subcommittee noted that there is a 10–20% serious disability rate for people who survive meningococcal disease, with those who experience significant complications requiring ongoing care and support.

5.7 The Subcommittee noted that mortality and morbidity were higher with MenC compared with meningococcal B (MenB) disease.

5.8 The Subcommittee noted that in New Zealand in 2016, the highest age-specific meningococcal rates were in infants aged under 1 year (18.6 per 100,000; 11 cases) and children aged 1–4 years (6.9 per 100,000; 17 cases).

5.9 The Subcommittee noted that by ethnicity, meningococcal disease rates tend to be highest in Pacific people followed by Māori. In New Zealand in 2016, meningococcal disease rates were 4.2 per 100,000 for Pacific people and 2.6 per 100,000 for Māori, compared with 1.6 per 100,000 for the total population.

5.10 The Subcommittee noted a systematic review and meta-analysis that investigated meningococcal carriage by age (Christensen et al. Lancet Infect Dis. 2010;10:853-61). The results identified carriage prevalence rates of 4.5% in infants, 23.7% in 19-year olds, and 7.8% in 50-year olds.

5.11 The Subcommittee noted that there are two meningococcal conjugate vaccines currently listed on the pharmaceutical schedule that are under consideration for widened access: a MenC conjugate vaccine (NeisVac-C) and a meningococcal ACYW-135 conjugate vaccine (Menactra).

5.12 The Subcommittee noted that both NeisVac-C and Menactra are funded for small sub-populations of patients who are considered to be high-risk; up to three doses and a booster every 5 years are funded for patients pre- and post-splenectomy and those with functional or anatomic asplenia, HIV, complement deficiency (acquired or inherited), or pre- or post-solid organ transplant; one dose for close

contacts of meningococcal cases; and two doses for bone marrow transplant patients and for patients following immunosuppression (due to steroid or other immunosuppressive therapy for a period of greater than 28 days).

5.13 The Subcommittee noted that PHARMAC was currently reviewing vaccine criteria regarding immunosuppression to ensure criteria refer to pre-elective immunosuppression lasting longer than 28 days as well as following immunosuppression (Immunisation Subcommittee recommendation October 2016). The Subcommittee also noted that PHARMAC was reviewing the vaccine criteria to include patients who have been infected with meningococcal bacteria (Immunisation Subcommittee recommendation July 2017).

5.14 The Subcommittee noted the results of the MenC vaccination program carried out in the UK. It was noted that the initial program included doses at 3 months, 1 year, and a booster dose at 14 years. One year after the vaccine was introduced carriage rates dropped by 71% in adolescents and young adults. The Subcommittee noted that in 2015, the MenC vaccine was replaced with a MenACYW vaccine for the adolescent and first year university boosters due to the reported increase in MenW cases. Recent data indicate that since the introduction of the MenACYW vaccine, MenY carriage has decreased by 39%. The Subcommittee noted that once herd immunity was established, the 3-month dose was removed from the schedule in 2016. The Subcommittee considered that invasive MenC disease is now rare in the UK.

5.15 The Subcommittee considered that the evidence from the UK program suggests that a dose at 3 months of age would not be a necessary component of a universal MenC vaccination program. The Subcommittee considered that herd immunity would provide adequate protection provided there was good uptake.

5.16 The Subcommittee considered that neither NeisVac-C or Menactra would be associated with additional health benefit in an epidemic outbreak situation and for infants under 1 year of age who were at high risk (e.g., close contact of meningococcal case) as they are already funded.

5.17 The Subcommittee considered that MenACYW (Menactra) vaccine offered additional health benefit over NeisVac-C as it provides protection against four strains. The Subcommittee noted that for children aged 9–23 months, two doses of Menactra were required at least 3 months apart. The Subcommittee considered that if universal childhood vaccination was implemented, this would require a change to the current immunisation schedule to introduce an additional visit at 12 months of age. The Subcommittee considered that if other Schedule changes were also made, such as funding MenB, then a 12 month visit to deliver varicella, MenACYW and MenB would be suitable.

5.18 The Subcommittee considered that the patient population that would benefit most from MenC vaccination is adolescents. The Subcommittee considered that the evidence for health benefits from herd immunity with MenC vaccines was strong, and therefore universal immunisation would be optimal; however, it was noted that MenC is rare at this time.

5.19 The Subcommittee considered that PHARMAC staff estimates of the patient group size for people aged 13-19 living in close living situations was low. Members requested that PHARMAC staff provide updated group estimates for consideration at a future meeting. Members considered that the group size estimates for children aged <1 year and 1 to 4 years were acceptable.

5.20 The Subcommittee considered that MenC infection disproportionately affects Māori, Pacific people and other groups already experiencing health disparities relative to the wider New Zealand population.

5.21 The Subcommittee considered that MenC estimated vaccine uptake would be: 20-30% for adolescents in close living situations, 90% for children aged 1-4 years and 90% for infants.

5.22 The Subcommittee considered that it agreed with the dosing schedules estimated by PHARMAC staff as follows for each group:

- 1 primary dose with a booster 5 years later for close living groups aged 13 to 19 years;
- 1 primary dose with a booster after 2 to 3 years for children aged 1 to 4 years;
- 2 doses in the first 12 months and a booster in the second year for infants aged <1 year.

5.23 The Subcommittee noted that adding an additional immunisation schedule visit would cost approximately an additional $1.2 million for vaccination claims, although the claim costs would be apportioned across all the vaccines delivered at that visit.

5.24 The Subcommittee considered that if a MenC vaccine was to be listed in the Pharmaceutical Schedule for universal infants immunisation, children aged 1 to 4 years and adolescents in close living situations, a quadrivalent meningococcal vaccine would be the most appropriate vaccine for New Zealand's epidemiology, however the Subcommittee deferred making a recommendation for the listing of meningococcal C vaccine. Members considered that they would like to see more epidemiological data for meningococcal disease to determine if it would be more effective to target access to close living situations or have universal immunisation with a dose for adolescents. The Subcommittee requested that PHARMAC staff provide recent epidemiological data to consider at the next meeting.

5.25 The Subcommittee considered that meningococcal C vaccine should not be listed in the Pharmaceutical Schedule for use during declared epidemics. Members considered that PHARMAC should assess such situations on a case-by-case basis.

6 Meningococcal B Vaccine (Bexsero)

Application

6.1 The Subcommittee reviewed the application from GSK Ltd for the meningococcal B vaccine, 4CMenB (Bexsero®), for universal childhood vaccination on the National Immunisation Schedule.

Recommendation

6.2 The Subcommittee **recommended** that 4CMenB be funded for universal infant vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a medium priority.

6.3 The Subcommittee **recommended** that 4CMenB be funded with a medium priority for high risk groups and close contacts, based on high clinical need.

Discussion

6.4 The Subcommittee noted that the rate of invasive meningococcal disease (IMD) in New Zealand in 2016 was 1.6 per 100,000 population, which was higher than in comparable countries, including the United States and England.

6.5 The Subcommittee noted that in New Zealand in 2016, 70% of meningococcal cases were serogroup B, 12% of cases were serogroup C, and 18% of cases were serogroups W or Y.

6.6 The Subcommittee noted that meningococcal B (MenB) disease disproportionately affects infants under 1 year of age, and Māori and Pacific Island populations (rates of 2.6 per 100,000 population and 4.2 per 100,000 population, respectively over the period 2007-2016). The Subcommittee noted that this disparity is less pronounced in more recent years.

6.7 The Subcommittee noted that 4CMenB is a multicomponent meningococcal group B vaccine containing purified recombinant meningococcal protein antigens consisting of four highly immunogenic components: three recombinant outer membrane proteins (neisserial heparin binding antigen [NHBA], neisserial adhesin A [NadA], and factor H binding protein [fHbp]) and outer membrane vesicles derived from *Neisseria meningitidis* group B strain NZ98/254.

6.8 The Subcommittee noted that 4CMenB is not yet approved by Medsafe, but that an application was submitted to Medsafe for priority assessment in December 2017.

6.9 The Subcommittee noted that 4CMenB has been licensed in a number of countries based on immunogenicity and safety data, but that no efficacy trial has been conducted. Members noted that not all B strains would be covered by the vaccine.

6.10 The Subcommittee considered that there was some potential for cross-protection against non-B serogroups with 4CMenB, as the antigens it contains are proteins that could be present on the surface of any meningococci rather than the type-specific polysaccharide capsule. The Subcommittee considered that the primary focus has

been on the current meningitis W outbreak strain as it contains the nadA gene, but that that there may be cross-protection against other serogroups as well. The Subcommittee also noted the previous evidence indicating the MeNZB vaccine was associated with reduced rates of gonorrhoea; possibly attributable to the 80-90% homology between *N. gonorrhoeae* and *N. meningitidis* (Petousis-Harris et al. Lancet. 2017;390:1603-1610).

6.11 The Subcommittee noted that the Meningococcal Antigen Typing System (MATS) assay has been developed to predict strain coverage. The MATS assay predicts that a strain was covered if it fits one of two criteria: sufficient expression of at least one protein antigen (fHbp, NadA, NHBA) as determined by ELISA, or the PorA gene is matched to that which is in 4CMenB. The Subcommittee noted that the supplier suggests that the MATS assay may underestimate strain coverage by 4CMenB. The Subcommittee considered strain coverage was likely to change over time, and that as MATS assay is not available in New Zealand, ongoing surveillance would be needed to judge likely strain coverage.

6.12 The Subcommittee noted a Phase 3, observer-blind, randomised controlled trial that investigated the effects of meningococcal quadrivalent glycoconjugate (MenACYW-CRM) or serogroup B (4CMenB) vaccination on meningococcal carriage rates in individuals between 18–24 years of age (Read et al. Lancet. 2014;384:2123-31). The trial included 2954 university students who were randomly assigned 1:1:1 to 4CMenB (two doses), MenACYW-CRM (one dose vaccine, one dose placebo), or control (Japanese encephalitis vaccine; two doses). The Subcommittee noted that the results demonstrated that from three months after the second vaccination, 4CMenB was associated with a 26.6% reduction in carriage of capsular groups BCWY compared with control. The Subcommittee considered that while this was a modest result, it indicates that 4CMenB may be effective in serogroups other than B. The Subcommittee noted that there was no effect on carriage reduction at one month after the second vaccination.

6.13 The Subcommittee considered the reactogenicity results of a Phase 2b, open-label, randomised trial that investigated the immunogenicity and reactogenicity of 4CMenB with or without routine infant vaccines (Gossger et al. JAMA. 2012;307:573-82). The Subcommittee noted that between 51% – 61% of infants developed a fever of ≥38.0°C after 4CMenB and routine vaccines were administered together, compared with 23% – 36% when routine vaccines were administered alone.

6.14 The Subcommittee considered that the fever associated with 4CMenB usually peaks 6 hours after administration and subsides within 24-48 hours, and that prophylactic paracetamol significantly decreases the rate of fever after vaccination. The Subcommittee noted that in the United Kingdom it is recommended that infants receive three doses of paracetamol following 4CMenB vaccination.

6.15 The Subcommittee noted several other studies that have investigated the consequences of the reactogenicity of 4CMenB.

a. A self-controlled case series that used linked routinely collected healthcare data to assess the risk of hospitalisation with fever following administration of the 4CMenB vaccine in infants under one year of age in Scotland (Murdoch H, et al. Arch Dis Child. 2017;102:894-898). The Subcommittee noted that

there was an increased risk of hospital admission with fever within 3 days of routine childhood immunisation at 8 and 16 weeks following the introduction of the 4CMenB vaccine.

b. A prospective audit study that investigated the management of infants aged 1 – 6 months attending regional paediatric emergency departments (ED) in Northern Ireland within 4 days of receiving 4CMenB (Kapur S, et al. Arch Dis Child. 2017;102:899-902). The Subcommittee noted that 0.8% of vaccinated infants attended the ED within 4 days of receiving 4CMenB.

c. A retrospective review of hospital records of infants aged 1 – 6 months presenting at EDs in Oxford with discharge diagnoses of vaccine reactions or non-specific conditions (Nainani V, et al. Arch Dis Child. 2017; doi: 10.1136/archdischild-2017-312941. [Epub ahead of print]). The Subcommittee noted that after the introduction of 4CMenB the rate of adverse events following immunisation (AEFI) reporting increased from 1.3 to 3.4 per 1000 immunisation episodes for infants aged 2 months, and from 0.14 to 1.13 per 1000 immunisation episodes for infants aged 4 months. No increase was seen at 3 months when 4CMenB was not given. AEFI-related hospital admissions, invasive investigation, and intravenous antibiotic use also increased following 4CMenB introduction.

6.16 The Subcommittee reviewed the immunogenicity results from a Phase2b, open-label, randomised trial that investigated the immunogenicity and reactogenicity of 4CMenB with or without routine infant vaccines (Gossger N, et al. JAMA. 2012;307:573-82). The Subcommittee noted that 4CMenB was immunogenic, and that the responses to routine vaccines given with 4CMenB were non-inferior to routine vaccines alone for all antigens except pertactin and serotype 6B pneumococcal polysaccharide. The Subcommittee noted that the routine vaccinations included PCV7 but not PCV10 or PCV 13 as used in New Zealand.

6.17 The Subcommittee noted the combined publication of two multicentre, Phase 3, primary and booster studies that investigated the immunogenicity and safety of 4CMenB administered concomitantly with routine vaccines (Vesikari T, et al. Lancet 2013;381:825-35). The Subcommittee noted that 4CMenB was immunogenic, that there was no clinically relevant interference with routine vaccines, and that reactogenicity increased when 4CMenB was given with routine vaccinations. The Subcommittee noted that the routine vaccinations included PCV7 but not PCV10 or PCV 13.

6.18 The Subcommittee noted an open-label, multicentre, Phase 3 study that evaluated the immunogenicity and safety of reduced 2+1 4CMenB administration schedule compared with a 3+1 schedule (Martinón-Torres F, et al. Vaccine. 2017;35:3548-3557). The Subcommittee noted that reduced infant schedules and catch-up series were immunogenic and safe. A follow-up analysis investigating the response 24 – 36 months post-vaccination found that antibody persistence was comparable between the 2+1 schedule and the 3+1 schedule (Martinón-Torres F, et al. ESPID 2017. ESP17-0987). Members considered that this may indicate that a 2+1 administration schedule was appropriate.

6.19 The Subcommittee considered that infants would benefit most from 4CmenB, particularly Māori and Pacific infants. The Subcommittee considered that the evidence for the immunogenicity and safety of 4CMenB is satisfactory, and that the early real-world efficacy data from the UK was promising. Members considered that 4CmenB would produce a health benefit for family or whānau through reducing quality of life losses for carers.

6.20 The Subcommittee considered that the assessment of 4CMenB should ideally include the possibility of a future epidemic, but it is not possible to predict the likelihood of a future epidemic. The Subcommittee considered that the assessment of 4CMenB could include the possibility of cross strain protection, although there is still some uncertainty about the extent of cross strain protection. Members considered that severity of disease varied among the Group B strains, but is less severe that Group C disease.

6.21 The Subcommittee considered that the funding of 4CMenB would be associated with a number of consequences to the health system, including a need for ongoing surveillance and a change in practice to include paracetamol as part of the administration protocol. The Subcommittee considered that the reactogenicity of 4CMenB may result in increased ED attendance and hospitalisation, as documented in the UK.

6.22 The Subcommittee considered that the applicant's assumptions of vaccine uptake of 75% in the first year, 85% in the second year and 92% in the third year were reasonable.

6.23 The Subcommittee noted that the application did not include the review Sadarangi et al. Clin Microbiol Infect. 2016; 22:s103-112.

6.24 The Subcommittee **recommended** that 4CMenB be funded with a medium priority for universal infant vaccination as part of the Infant Immunisation Schedule. The Subcommittee noted the reactogenicity issues with this vaccine. Members noted that adding 4CMenB to the infant schedule would incur significant costs to the health sector for vaccine costs and vaccination administration claims. Members noted that adding 4CMenB to the infant schedule would necessitate an additional immunisation visit at 12 months and changes to the infant schedule to ensure optimal vaccine combinations at each visit.

6.25 The Subcommittee **recommended** that 4CMenB be listed with a 2+1 dosing schedule.

6.26 The Subcommittee **recommended** that 4CMenB be funded with a medium priority for high risk groups and close contacts, based on high clinical need. The Subcommittee discussed the concept of conducting a pilot in an area with high rates of meningococcal disease to demonstrate whether it was possible to effectively target high risk areas.